REMARKS

A. Regarding the Amendments

By the present communication claim 100 has been amended and new claim 412 has been added to more particularly define Applicants' invention. As amended, the claims are supported by the specification and the original claims and add no new matter. For example, support for the phrase "substantially insoluble", as recited in claim 100, is found throughout the specification. In addition, as recited in new claim 412, support for "substantially flexible vesicles" is found in the specification at page 99, lines 1-16. Upon entry of the amendments, claims 100-103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356, and 412 are under consideration.

B. Rejections Under 35 U.S.C. § 103(a)

Claims 100-103, 127, 194-200, 203, 210-228, 294-300, 303, 310-329, 331-337, 347-356 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Grinstaff (U.S. Patent No. 5,498,421) in view of Wallach (U.S. Patent No. 4,853,228), Allen (U.S. Patent No. 5,620,689) and Ginsburg (U.S. Patent No. 5,656,442). For the following reasons, it is respectfully submitted that none of the cited references, either alone or in combination, disclose or suggest the formulations and methods set forth in the claim submitted herewith.

Presently amended claim 100 requires a formulation for therapeutic or diagnostic use comprising targeted gas-filled vesicles which comprise one or more membranes encapsulating an internal void that contains a substantially insoluble gas selected from the group consisting of perfluorocarbons and sulfur hexafluoride, said membrane comprising a phospholipid, and being substantially free of crosslinked proteins and polymers, and further comprising a conjugate that comprises a lipid, a linking group, and a targeting ligand,

wherein:

the linking group is a hydrophilic polymer that is covalently bound to both said lipid and said targeting ligand, and is selected from the group consisting of polyethylene glycol (PEG), polypropylene glycol, polyvinylalcohol, polyvinylpyrrolidone, and copolymers thereof, and wherein said targeting ligand is selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material.

None of the cited references, alone or in combination, disclose or suggest a formulation including vesicles that encapsulate substantially insoluble gases. Indeed, it is submitted that the insolubility of the encapsulated gases contributes to the stability of the vesicles described in the present application. In contrast, the primary reference, Grinstaff, merely describes highly crosslinked polymeric shells for delivery of bioactive agents, but clearly does not describe or suggest formulations including the vesicles described in the present specification. Instead, Grinstaff describes encapsulation of liquid perfluorocarbons. Those skilled in the art readily recognize that, in contrast to the present invention, Grinstaff's polymeric shells are not acoustically active due to the liquid that is encapsulated within the shell. In addition, Grinstaff's shells do not cavitate when subjected to ultrasonic radiation. To the contrary, Grinstaff applies ultrasonic energy to crosslink the polymer materials that ultimately form the rigid shells described therein.

In addition, present claim 412 distinguishes over Grinstaff by requiring a formulation for therapeutic or diagnostic use comprising targeted gas-filled vesicles, wherein said vesicles are substantially flexible and which comprise one or more membranes encapsulating an internal void that contains a gas selected from the group consisting of perfluorocarbons and sulfur hexafluoride, said membrane comprising a phospholipid, and being substantially free of crosslinked proteins and polymers, and further comprising a conjugate that comprises a lipid, a linking group, and a targeting ligand,

wherein:

the linking group is a hydrophilic polymer that is covalently bound to both said lipid and said targeting ligand, and is selected from the group consisting of polyethylene glycol (PEG), polypropylene glycol, polyvinylalcohol, polyvinylpyrrolidone, and copolymers thereof, and wherein said targeting ligand is selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material.

The presently claimed formulations include vesicles that are substantially free of crosslinking and therefore the membranes of the vesicles are substantially flexible. This flexibility provides unexpected advantages that are not disclosed or suggested by any of the cited references. For example, these flexible vesicles are readily able to slide through blood vessels and especially through capillaries, resulting in improved distribution throughout the vasculature. In addition, those skilled in the art recognize that rigid vesicles can lodge in the lungs or other organs and cause toxic reactions. In contrast to the present invention, Grinstaff's vesicles have rigid, highly crosslinked polymeric shells that encapsulate bioactive agents. Thus, it is clear that Grinstaff's vesicles could not provide the unexpected results achieved by the present invention.

For the reasons set forth above, it is respectfully submitted that the rejections under 35 U.S.C. 103(a) do not properly apply to the amended claims presented herein. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: October 21, 2003

Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

USPTO Customer Number 28213
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133